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Exposures to Pharmaceutical Dust at a Mail Order Pharmacy

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INTRODUCTION

Mail order pharmacies are the fastest growing sector of the U.S. prescription drug retail market. In 2004, they accounted for 6.1% of all prescriptions filled, which was an 18% increase over the previous year.(1) Although large volumes of prescriptions are filled at mail order pharmacies, the potential for employee exposures to pharmaceutical dust has not been fully evaluated. In 2010, the National Institute for Occupational Safety and Health (NIOSH) received a health hazard evaluation request from managers at a mail order pharmacy concerning potential pharmaceutical dust exposures to employees.

The mail order pharmacy was divided into two areas: (1) the pharmacy, where automatic dispensing machines were located and most prescriptions were filled, and (2) the warehouse, where other activities such as manual counting and replenishment of canisters were performed. Two brands of automatic dispensing machines were used for filling high throughput prescriptions: Baker (one large customized machine made by McKesson Corporation, San Francisco, Calif.) and Optifill (two smaller customized machines made by AmerisourceBergen, Valley Forge, Pa.). All three machines used gravity to dispense pharmaceutical tablets and capsules.

The Baker machine had an elevated platform where the canisters containing pharmaceuticals were loaded into the machine. The pharmaceuticals were fed from a canister into a cell below the platform. A conveyor belt on the outside of the machine carried a prescription bottle to the nozzle below the appropriate cell, and a valve in the cell opened to dispense the pharmaceutical into the bottle. The Baker machine filled approximately 10,000 prescriptions per day. Two pharmacy technicians maintained the Baker machine. Their responsibilities included freeing jams, identifying bottles that were not filled, and cleaning and repairing malfunctioning cells. The Baker canisters were refilled in the offline replenishment area in the warehouse where two or three pharmacy technicians dumped the appropriate pharmaceuticals from the original manufacturer packaged bottles into a funnel that fed into a labeled Baker canister.

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Canisters were situated on the outside of each of the two Optifill machines. A conveyor belt carried prescription bottles through the middle of either machine. A bottle stopped below one of the eight shared chutes in each machine. A canister dispensed the appropriate pharmaceutical into the chute that funneled into the bottle. The Optifill machines filled approximately 2000 prescriptions per day. Two pharmacy technicians replenished and repaired the Optifill canisters, which were then verified by a pharmacist.

Pharmacy technicians also filled prescriptions by hand in the special handling, hazardous drug, or manual count areas in the warehouse. Hazardous drugs are drugs known or suspected to cause adverse health effects from exposures in the workplace.[2,3] Warfarin was the primary pharmaceutical dispensed in the special handling area, while a variety of other pharmaceuticals were dispensed in the manual count areas. Baker canisters were also routinely cleaned in the warehouse using mainly detergent and water.

Use of personal protective equipment was sporadic among employees and included vinyl examination gloves or nitrile gloves, N95 filtering facepiece respirators, hair caps, and cloth aprons. We did not observe the presence or use of local exhaust ventilation for any of the processes.

METHODS

We conducted a multi-metric evaluation (1) to determine if and during which activities dust was released into the air, (2) to measure the concentration of the airborne dust, (3) to determine if the airborne dust contained pharmaceuticals, and (4) to identify and quantify specific active pharmaceutical ingredients (APIs) in the airborne dust. We visited the facility in April and December 2010. The information gathered during the first visit was used to develop our sampling methodology for the second visit. Here we present the methods and results of the second visit that took place over 3 days in December 2010. For complete results, see the health hazard evaluation report available at http://www.cdc.gov/niosh/hhe/reports/pdfs/2010-0026-3150.pdf.

We collected 25 each of total dust (37-mm-diameter closed-face cassette, 4 L/min) and inhalable dust (25-mm-diameter Institute of Medicine cassette, 2 L/min) air samples on 11 employees. Samples were positioned side-by-side in the employees' personal breathing zone (PBZ) and collected over the entire work shift (approximately 8 hr). Both the total and inhalable dust samplers contained tared polytetrafluoroethylene filters (1-μm pore size) that were analyzed gravimetrically. Due to its larger inlet, an inhalable dust sample collects more particles >30 μm in aerodynamic diameter than a closed-face total dust sample.[4]

Real-time particle count measurements were collected using an HHPC-6 (Hach Ultra Analytics, Inc., Loveland, Colo.) near the PBZs of the employees to identify specific tasks that resulted in increased particle counts (Figure 1). The types of tablets that were handled during these dust-releasing tasks were recorded. Managers and employees at the pharmacy also provided us with a list of tablets that were friable. Such tablets were uncoated mainly and, in many cases, were the generic version of a brand name pharmaceutical. Using this

information, we generated lists of APIs that could potentially be present on each total or inhalable dust sample filter.

Figure 2 shows the progression of the other analyses done on the total and inhalable dust sample filters after they were analyzed gravimetrically. We quantified lactose, a common inactive ingredient in pharmaceuticals, on the inhalable dust sample filters using an analytical method developed by BureauVeritas (Novi, Mich.). Total dust sample filters were analyzed using a desorption electrospray ionization/mass spectrometry (DESI/MS) system[5] to identify specific APIs on the filters by cross referencing mass-to-charge ratios with the lists of APIs handled at the facility. Four total dust sample filters were not further analyzed because we did not have information to indicate which APIs could be present on them.

We selected five inhalable dust samples for quantitation of lisinopril, which was chosen because the analytical method developed by Bureau Veritas required dissolution in water, and the inhalable dust samples were already dissolved in water for the lactose analysis. In addition, lisinopril has a relatively low manufacturer's exposure control band of 1 to <10 $\mu g/m^3$.[6] We also selected two total dust air samples for quantitation of warfarin using NIOSH Method 5002.[7] We chose to analyze for warfarin because it was the predominant drug handled by the employees in the special handling area. The analytical methods for lactose and lisinopril are summarized in the health hazard evaluation report. We used Microsoft Excel for performing basic statistics.

RESULTS

Peaks in particle counts were observed during the cleaning of Baker cells and replenishment of Baker canisters (data not shown). Using our recorded observations, we identified the APIs that were handled during these peaks in particle counts. Figure 3 summarizes the PBZ inhalable dust (ranging from 110–800 $\mu g/m^3$), total dust (ranging from 6–260 $\mu g/m^3$), and lactose concentrations (ranging from 0.94–63 $\mu g/m^3$) by process and location; standard deviations are represented by error bars. Area air concentrations (measured in the non-production areas of the pharmacy) are also included in Figure 3 to show the relatively low background levels of dust and lactose. Area air concentrations of lactose in the non-production areas of the pharmacy were significantly lower ($P < 0.001$) than the PBZ concentrations measured on employees in the production areas.

The average inhalable dust concentrations were 1.3 to 3.7 times higher than the average total dust concentrations measured on the same employees. The highest average total and inhalable dust exposures were measured in the PBZs of employees who did offline replenishment of Baker canisters, hand filling of prescriptions (manual count), online replenishment of Optifill canisters, and cleaning of Baker cells. Employees doing these tasks, as well as the hand filling of prescriptions (special handling), also had the highest average PBZ concentrations of lactose.

APIs were detected on 17 of 19 total dust sample filters analyzed by DESI/MS. The 17 APIs identified on these filters are shown in Table I. Five other APIs were identified on three total dust sample filters collected during the first visit (data not shown). The PBZ concentrations

of warfarin (n = 2), measured during the hand filling of warfarin prescriptions (special handling), ranged from 0.50–0.64 $\mu g/m^3$. Similar levels (0.19–3.8 $\mu g/m^3$, n = 3) were measured during the first visit. These levels are well below the NIOSH recommended exposure limit, the Occupational Safety and Health Administration permissible exposure limit, and the ACGIH® threshold limit value (TLV®) of 100 $\mu g/m^3$.[8,9] Likewise, PBZ concentrations of lisinopril (n = 5), measured during different processes, ranged from non-detectable to 0.44 $\mu g/m^3$ and were well below the manufacturer's exposure control band of 1 to <10 $\mu g/m^3$.[6]

DISCUSSION

The correlation of tasks (i.e., cleaning of Baker cells and replenishment of Baker canisters) with peaks in real-time particle counts suggests that pharmaceutical dust was released into the air where it could be inhaled by employees. Compared with a closed-face total dust sampler, an inhalable dust sampler, which has a larger inlet, has been shown to undersample particles larger than 30 μm in aerodynamic diameter.[4] Thus, the higher levels of inhalable dust compared with total dust suggest that some particles >30 μm in aerodynamic diameter were released. These larger particles settle quickly to the ground but when inhaled they are likely to be captured in the upper respiratory tract.[10] Although not presented here, respirable dust concentrations measured during the first visit were very low (at or below detection limits). Therefore, much of the pharmaceutical dust that was released probably did not stay suspended in the air for more than a few seconds. Hence, the inhalation exposure potential is likely far greater for the employees who undertake tasks that generate pharmaceutical dust than other employees (even those in the same general area). The highest PBZ concentrations of total dust, inhalable dust, and lactose were all measured on employees who performed duties that could generate pharmaceutical dust.

Occupational exposure limits (OELs) for general dust or particles not otherwise regulated are only applicable when the dust particles are biologically inert and are insoluble in water.[8] Pharmaceutical dust does not meet these criteria because APIs are designed to elicit biological responses, and most tablets are water soluble. Hence, inhalable pharmaceutical dust is biologically relevant because it can be absorbed anywhere in the respiratory system. Our data confirm that at least some of the dust we collected on air samples came from pharmaceuticals. Lactose, a common inactive ingredient in pharmaceuticals, was present in all inhalable dust air samples, and specific APIs were identified in most of the total dust air samples. The two APIs (warfarin and lisinopril) we selected for quantitation in air were present in one or more air samples, but the PBZ concentrations did not exceed their respective OEL or exposure control band.

The pharmacy stocked 61 hazardous drugs according to the NIOSH list,[3] 35 of which were tablets and therefore potentially capable of producing dust. Although we did not measure employee exposures during the hand filling of hazardous drug prescriptions, this process could present a substantial health risk to employees if proper safeguards are not in place. Exposures to hazardous drugs, even at low levels, can lead to serious health effects, including skin rashes, reproductive problems, and possibly cancer.[2] The pharmacy managers provided us with a copy of their standard operating procedures, which included

provisions for wearing gloves and cleaning up spills. No other control measures were listed. Although the guidelines in the NIOSH Alert, *Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings*, are intended primarily for oncology clinics and hospital pharmacies, they could be adapted for this and other mail order pharmacies.

Ideally, we should have quantified PBZ concentrations to more of the APIs that we identified in air. However, we did not have access to analytical methods or manufacturer's OELs for all of these APIs. Also, because APIs may require different extraction solvents, it is difficult to analyze for all APIs that might be collected on an air sample. Although pharmaceutical companies have established analytical methods and OELs or exposure control bands for many of the drugs they manufacture, not all are publicly available (e.g., provided in safety data sheets) or were provided to the mail order pharmacy we evaluated. Access to these methods and OELs or exposure control bands is necessary to conduct comprehensive exposure assessments in this growing industry. This information may be provided by manufacturers on request.

On the basis of the data we were able to gather, we believe it is prudent to reduce exposures during tasks that generate pharmaceutical dust. Employees who clean cells, replenish canisters, and hand fill prescriptions with friable tablets are potentially exposed to low levels of APIs that they are not prescribed. Some individuals may have allergies to specific APIs or take medications that could interact with APIs. Moreover, they are inhaling these APIs rather than ingesting them, which could change how the chemical affects the body. If exposed to multiple APIs, synergistic or additive health effects could be possible. In addition, pharmaceutical dust may settle on work surfaces and clothing. If employees do not wear gloves or wash hands before eating or using tobacco products as mandated, they could ingest APIs. Dermal absorption is also possible depending on the chemical makeup of APIs. For employees engaged in tasks that generate pharmaceutical dust, secondary exposure to family members may occur if personal clothing becomes contaminated with pharmaceutical dust and is worn at home. Children may be especially susceptible to adverse health effects from API exposures.[11]

We provided a number of recommendations to the mail order pharmacy managers to minimize pharmaceutical dust exposures. These recommendations included requiring employees to use local exhaust ventilation when cleaning cells, replenishing canisters, and hand filling hazardous drug prescriptions. We also recommended providing disposable gowns (or gowns that are kept at the pharmacy and professionally laundered) for employees to wear during work. The health hazard evaluation report provides a full list of our recommendations. However, further study is warranted to plan, implement, and test the efficacy of the recommended controls.

CONCLUSION

To our knowledge, this is the first evaluation of pharmaceutical dust exposures at a mail order pharmacy. Our data show that mail order pharmacy employees can be exposed to dust containing APIs, particularly when they clean cells, replenish canisters, or hand fill

prescriptions. More comprehensive evaluations are needed in this growing industry to determine the extent of exposures to APIs, including hazardous drugs, and to determine the best control measures and practices for minimizing such exposures.

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FIGURE 1.
Using a real-time particle meter to measure particle counts near the PBZ of an employee cleaning a Baker cell

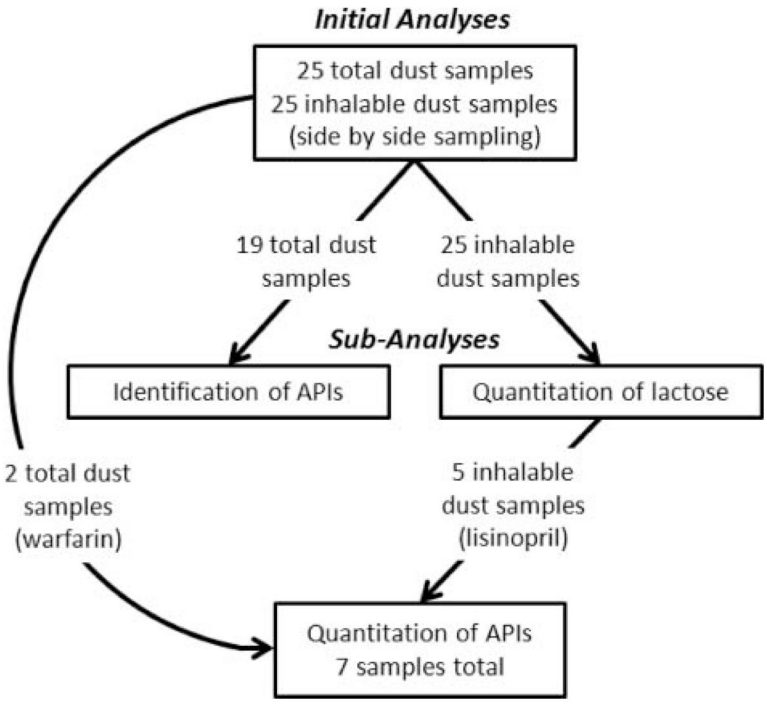

FIGURE 2.
Flow chart showing the subanalyses performed on the total and inhalable dust sample filters

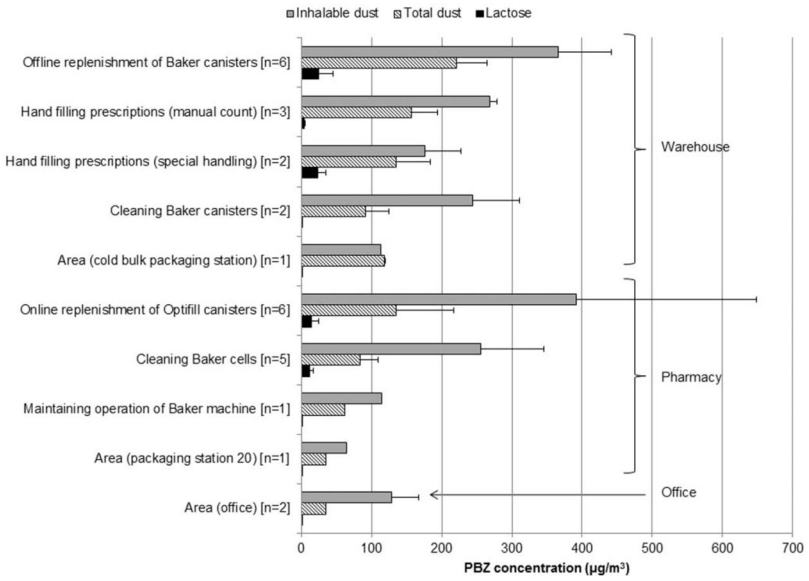

FIGURE 3.

Summary of average work-shift PBZ concentrations of inhalable dust, total dust, and lactose by process and location. Error bars represent one standard deviation.

TABLE I

APIs Identified on the Total Dust Air Samples Using DESI/MS Analysis

Process	Employee ID	Sample Day	Benazepril	Bethanechol	Buspirone	Doxazosin	Glipizide	Hydralazine	Lamotrigine	Levodopa	Lisinopril	Meclizine	Metformin	Methocarbamol	Oxybutynin	Promethazine	Sotalol	Trazadone	Venlafaxine
Cleaning Baker cells	7	1															X		
		2															X	X	
		3			X			X					X						
	21	1							X	X	X								
		2		X									X		X				
Offline replenishment of Baker canisters	9	1														X			
		2											X	X				X	
	18	1												X				X	
	20	1										X							
		3					X												
	24	3					X											X	
Online replenishment of Optifill canisters	16	1				X			X			X							X
		2							X			X							X
		3										X							
Checking online replenishment of Optifill canisters	6	1							X			X							
		3	X						X			X							
Hand filling of prescriptions (manual count)	17	1																	X

Note: X denotes that the compound was identified in that sample.